

THE BRITISH JOURNAL OF DERMATOLOGY

OCTOBER 1961

CONTROLLED TRIALS OF TWO ORAL ANTIPRURITIC DRUGS, TRIMEPAZINE AND METHDILAZINE.

M. A. SMITH AND M. P. CURWEN.

St. Bartholomew's Hospital, London.

BOTH pharmacological and psychological factors play a part in the treatment of pruritus. Several oral antipruritic drugs in the phenothiazine group of compounds have been produced during the past few years, but as they are relatively expensive and potentially toxic (Clendenning, Kress and Rauschkolb, 1960) it is clearly desirable to establish their merits in comparison with cheaper and blander substances. This paper describes two controlled clinical trials designed to test the efficacy of trimepazine tartrate and methdilazine hydrochloride compared with an inert placebo.

INVESTIGATION.

Sequential analysis.—Several trials using the method of sequential analysis have recently been described (Snell and Armitage, 1957; Thomson, 1958 and Watkinson, 1958) and it is not proposed to give a full description here. The chief purpose of the method is to enable a trial to be carried out without determining in advance the number of patients to be included. It may be possible, if there is a clear difference between the treatments, to stop the trial after only a small number of patients has been tested. The method is particularly suitable for relatively minor complaints where a single criterion can be used to assess the value of the treatment and where it is not required to determine the effects of treatment in various sub-groups.

In the two double-blind trials described here, patients were treated successively with the active drug and the placebo and then asked which (if either) gave the better relief to the itching. As each preference was expressed it was recorded on a chart constructed by Armitage's (1957) method (Figs. 1 and 2). Starting from the shaded square, a cross was entered to the "north-east" for a result in favour of the active drug and to the "south-east" for the placebo; no entry was made if there was no preference. As soon as one of the boundaries was crossed, the trial was stopped, the result being regarded as "significant" or "not significant" as indicated on the chart.

The chart used here is constructed in such a way as to give a 5% level of significance to a positive result and to ensure (at 95% probability) that such a result will occur providing that at least 80% of the population prefer one treatment.

First trial: trimepazine tartrate.—A series of pairs of pill-boxes marked 1a, 1b; 2a, 2b, etc., was prepared, each box containing either 28 tablets of trimepazine

tartrate (10 mg.) or 28 inert tablets identical in appearance, the active drug being allotted to *a* or *b* according to a random sequence of which the key was held by M.P.C.

All patients seen in the out-patient clinic by M.A.S. and with a history of pruritus of at least one month's duration were accepted into the trial. Each patient was given the *a* box at the start of the trial and was advised to take four tablets daily spaced as evenly as possible throughout the day and preferably before meals; if the tablets upset him in any way the patient was advised to reduce the dose to such as he could manage without ill effect. Those patients who enquired what side effects there might be were told that some drowsiness might be encountered.

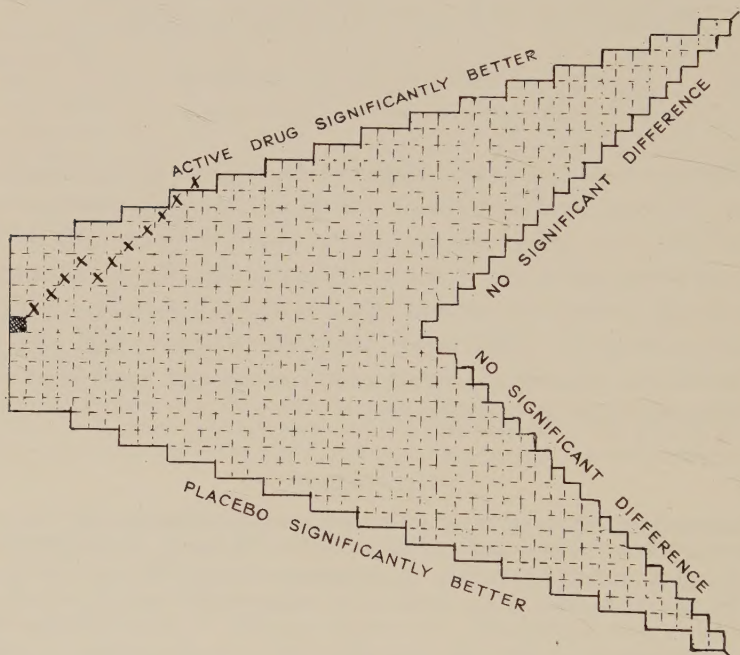


FIG. 1.—Trial of trimeprazine, sequential chart.

A record of any rash visible at the time was made; no local treatment was prescribed for those not already having it and the same local treatment as before was continued in the others. The patients were given the tablets in the clinic and asked to return the following week. On the return visit a note was made of the severity of the pruritus and the appearance of the rash, when present, and the patient was given the *b* box of tablets and asked to continue the same treatment for another week and then to report again. Those patients who had not taken all their tablets at the end of the first week were told to start on the second box nevertheless.

At the end of the second week the patient was first asked whether he felt less itching in either week compared with the other week, and then the skin was examined and the patient was questioned about any side effects. As soon as the patient expressed a preference for one week or the other the "code" was broken and the sequential chart marked as shown in Fig. 1.

The boundary was in fact crossed after 11 patients had given a definite preference (10 for the active drug and 1 for the placebo) ; at this point the trial was stopped and it was judged that the proportion of patients who preferred the active drug was significantly greater than that of those who preferred the placebo. From this point no new patients were admitted into the trial but those who were already in it were allowed to complete it and are included in the following analysis.

Second trial: *methdilazine hydrochloride.*—Materials and methods were the same as before. The active tablets contained 8 mg. of methdilazine hydrochloride and the dose was three tablets daily. The sequential chart was marked as in Fig. 2.

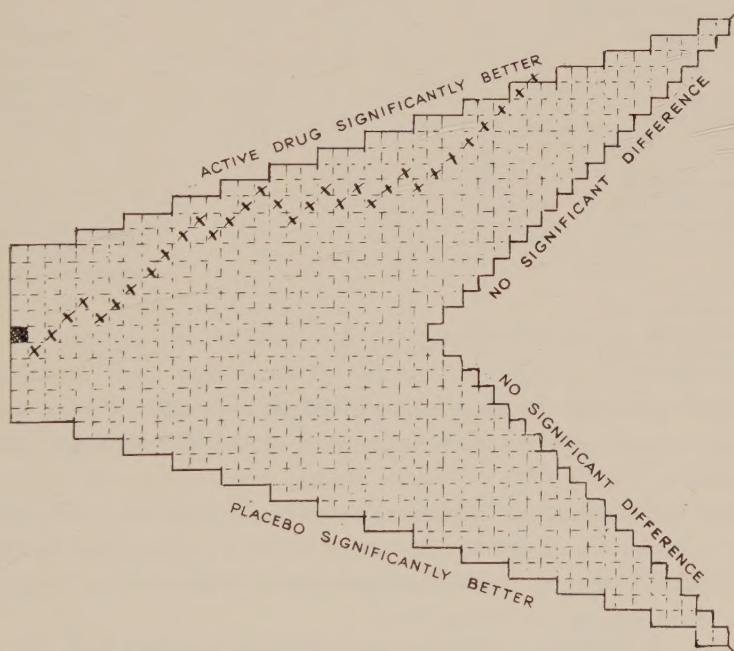


FIG. 2.—Trial of methdilazine, sequential chart.

Table I gives the results according to the diagnosis and the order of administration. The two patients who preferred the placebo tablets reported a slight preference only and in each instance had taken the active tablets first, so that it might be suggested that improvement was initiated by the active drug and sustained by the placebo.

Of the five patients who failed to complete the trial, one had an attack of paroxysmal tachycardia, from which he had suffered in the past, while taking the placebo, one said he did not wish to take tablets when he reported at the end of the first week, one did not report at the end of the first week while taking the active drug and two failed at the second week, one having started with the active drug and one with the placebo.

RESULTS.

First trial (trimeprazine).—There were 27 patients in the trial, 16 men and 11 women aged from 20 to 78 years.

TABLE I.—*Trial of Trimeprazine.*

	Number of patients.	Preferred.		No preference.	Did not complete trial.
		Active drug.	Placebo.		
Total	27	11	2	9	5
Order of administration :					
Active drug first	14	5	2	4	3
Placebo first	13	6	—	5	2
Diagnosis :					
Eczema : total	17	8	1	6	2
atopic	1	1	—	—	—
discoid	2	2	—	—	—
endogenous	2	2	—	—	—
hypostatic	1	—	—	1	—
lichen simplex	7	2	—	3	2
seborrhoeic	4	1	1	2	—
Lichen planus	3	—	1	—	2
Psoriasis (flexural)	2	—	—	2	—
Senile pruritis	3	1	—	1	1
Urticaria (chronic)	2	2	—	—	—

Of the nine patients who found no difference between the two weeks, three reported an overall improvement in pruritus during the trial and six were as bad or worse.

The chief side effect of trimeprazine was drowsiness. The only other symptoms complained of during the first trial were paroxysmal tachycardia in one patient and dyspepsia in another, the former while taking the placebo and the latter while taking the active drug.

Second trial (methdilazine).—There were 72 patients in this trial, the boundary being crossed after 32 patients had given a definite preference (Fig. 2). The ages were from 17 to 77 years, with 43 men and 29 women. The conditions from which they suffered and their response to treatment are shown in Table II.

Of the seventy-two patients, twelve did not complete the trial : six failed to attend after the first week, five of whom had been taking the active drug and one the placebo, two did not come after the second week, one of whom started with the active drug and one with the placebo and four did not wish to take the tablets.

Of the sixty patients who completed the trial, twenty-seven expressed no preference between the drug and placebo and thirty-three did so (Table II), twenty-four preferring the active drug and nine the placebo.

The nine who preferred the placebo were as follows : four with lichen simplex, two with eczema of the palms, one each with lichen planus, discoid eczema and senile pruritis : five took the placebo during the first week and four during

TABLE II.—*Trial of Methdilazine.*

	Number of patients.	Preferred.		No preference.	Did not complete trial.
		Active drug.	Placebo.		
Total	72	24	9	27	12
Order of administration :					
Active drug first . .	36	10	4	14	8
Placebo first	36	14	5	13	4
Diagnosis :					
Eczema : total . . .	55	17	7	21	10
atopic	2	2	—	—	—
discoïd	5	—	1	3	1
endogenous	16	8	2	5	1
hypostatic	3	1	—	1	1
lichen simplex . . .	20	4	4	8	4
seborrhoeic	8	2	—	3	3
solar	1	—	—	1	—
Lichen planus . . .	4	1	1	2	—
Pruritus	2	1	—	1	—
Psoriasis (flexural) .	3	2	—	1	—
Senile pruritus . . .	4	1	1	1	1
Urticaria (chronic) .	4	2	—	1	1

the second. Among the twenty-four preferring the active drug, ten took it during the first week and fourteen during the second. Considering all the preferences together fifteen preferred the first week of the trial, whether taking active drug or placebo, and eighteen preferred the second.

Apart from drowsiness, one patient reported difficulty in accommodation while taking the active drug and another had headaches with both active drug and placebo.

Both trials.—Drowsiness was the chief side effect of both drugs (Table III).

TABLE III.—*Drowsiness and Patients' Preferences.*

	Total patients.	Number of patients reporting drowsiness with			
		Active drug only.	Placebo only.	Both tablets.	Neither tablet.
Trimeprazine trial :					
Patients preferring { active drug . .	11	5	1	—	5
{ placebo	2	1	—	—	1
{ neither	9	4	—	1	5
Total	22	10	1	1	10
Methdilazine trial :					
Patients preferring { active drug . .	24	8	—	3	13
{ placebo	9	2	—	1	6
{ neither	27	6	—	—	21
Total	60	16	—	4	40

Combining both trials, there were twenty-six patients (32%) who experienced drowsiness with the active drug alone, one with the placebo and five with both

drug and placebo. The latter figures are to be expected in view of the fact that some patients were warned that they might experience a little drowsiness.

There is some evidence that there was less drowsiness with methdilazine than with trimeprazine but as trimeprazine seemed to be slightly more active as an antipruritic, both effects may be due to the doses given being not entirely comparable, so that 40 mg. of trimeprazine is possibly more potent than 24 mg of methdilazine in a daily dose. A few patients in both trials were almost prostrated with only two tablets daily of the active drug and as in the case of the antihistamines, a small proportion of people seem to be especially subject to this side effect. From Table III it will be seen that the antipruritic effect of trimeprazine was as marked in those patents who did not complain of drowsiness as in those who did ; whereas with methdiazine, out of 20 patients who were drowsy on the active drug, 11 (55%) preferred it to the placebo ; whereas of the 40 who were not drowsy, only 13 (33%) preferred the active drug. This suggests that in the case of methdilazine the two effects were more closely linked than in the case of trimeprazine, but the small number of cases in the first trial should be borne in mind.

The trials were designed on the basis of the patients' preference, but a record was also kept of the appearance of the rash, when present, in terms of improvement or no improvement compared with the previous week. Table IV compares

TABLE IV.—*Objective Improvement and Patients' Preferences.*

		Total patients.	Number of patients showing objective improvement with			
			Active drug only.	Placebo only.	Both tablets.	Neither tablet.
Trimeprazine trial :						
Patients preferring	{ active drug .	11	4	—	1	6
	{ placebo .	2	—	—	—	2
	{ neither .	9	1	—	1	7
Total		22	5	—	2	15
Methdilazine trial :						
Patients preferring	{ active drug .	24	9	—	4	11
	{ placebo .	9	—	—	2	7
	{ neither .	27	2	—	12	13
Total		60	11	—	18	31

this objective assessment with the patient's preference. There was no case in either trial where objective improvement was recorded with the placebo and not with the active drug. Of the eleven patients preferring the placebo in both trials, there was no objective improvement in either week in nine and an improvement in both weeks in two. There were sixteen patients (in both trials) who showed an objective improvement with the active drug only, six of whom took the active drug during the first week and ten during the second

week. In more than half the cases there was no objective improvement with either drug. Further analysis indicated that a similar proportion showed objective improvement whether drowsiness was reported or not.

DISCUSSION.

In the first trial, 85% of patients expressing a choice preferred trimeprazine tartrate to the placebo and in the second 72% preferred methdilazine hydrochloride to the placebo. We have concluded that these proportions could not have occurred by chance had the drugs tested been inert, and that both possess, as judged by the patients, a real anti-pruritic effect. No statistical significance can be attached to the slightly higher rate of preferences for trimeprazine tartrate compared with methdilazine hydrochloride, but as the former produced slightly more drowsiness as well it is probable that the doses given were not quite comparable. However the effect of these two drugs was unpredictable in any one patient, both in regard to the antipruritic effect and the production of drowsiness, there being wide variation in individual susceptibility. In subsequent practice it was found that some patients were benefited by one of the drugs and not the other and, as in the case of the antihistamines, it would seem worth while to try a number of similar compounds if the first does not prove successful.

In each trial, barely more than half the patients who completed the treatment expressed a preference (the proportions were 59% and 55% respectively), and in those who did this preference was not always pronounced. Probably not much more than a quarter of the patients benefited from these drugs.

These figures are borne out by analysis of the objective improvement as recorded by the physician. In the first trial, 7 patients (32%) showed objective improvement with the active drug and in the second 29 patients (48%). However, the second trial contained more people who showed objective improvement with both active drug and placebo and if these patients are omitted the proportion is about a quarter for both drugs.

The true incidence of drowsiness, after allowing for the effect of suggestion, is probably of the order of 20-30%. Table III shows that there is no evidence that drowsiness influenced the preferences in the case of trimeprazine, although the numbers are small, but in the case of methdilazine there is a possibility that it did to a small extent. There was no association between objective improvement and drowsiness.

Several explanations suggest themselves for the patients who preferred the placebo tablets: the natural course of the skin complaint may have been responsible, the patients may have wished to give a definite preference where none existed, or the side effects, while taking the active drug, may have evoked a preference for the placebo.

It is concluded that both trimeprazine and methdilazine can be recommended for the symptomatic treatment of patients with pruritus, and that such treatment may also result in the breaking of the itch-scratch cycle with consequent improvement.

SUMMARY.

A double-blind sequential trial was conducted in which patients with chronic pruritus were treated for one week with trimeprazine tartrate and for one week with an inert placebo. Out of twenty-two patients, eleven preferred the active drug, two the placebo and nine had no preference.

In a similar trial of methdilazine hydrochloride, out of sixty patients twenty-four preferred the active drug, nine the placebo and twenty-seven had no preference.

It was concluded that both drugs had a real antipruritic effect, although the proportion of such patients likely to be benefited may not be more than a quarter.

Drowsiness was the only common side effect and was reported in approximately a third of the patients in the trials. There were no other complications of treatment.

Thanks are due to May and Baker Ltd. for supplying the trimeprazine tartrate ("Vallergan") tablets and placebos, and to British Drug Houses Ltd. for the methdilazine hydrochloride ("Dilosyn") tablets and placebos.

REFERENCES.

- ARMITAGE, P. (1957) *Biometrika*, **44**, 9.
CLEDENNING, W. E., KRESS, M. A. and RAUSCHKOLB, E. W. (1960) *Arch. Derm., Chicago*, **82**, 533.
SNELL, E. S. and ARMITAGE, P. (1957) *Lancet*, **i**, 860.
THOMSON, J. B. (1958) *Brit. med. J.*, **ii**, 1140.
WATKINSON, G. (1958) *Ibid.*, **ii**, 1077.
-
-

THE TREATMENT OF CHRONIC DISCOID LUPUS ERYTHEMATOSUS WITH A COMBINATION OF ANTIMALARIAL AND CORTICOSTEROID DRUGS.

SUZANNE ALEXANDER AND M. A. COWAN.

Department of Dermatology, The Radcliffe Infirmary, Oxford.

THE treatment of chronic discoid lupus erythematosus (chronic L.E.) has been revolutionized by the introduction of antimalarial drugs (Prokoptchouk, 1940 ; Page, 1951) ; 80% of cases are controlled, but relapse is frequent when treatment is stopped (Gold, 1960). Neither control nor relapse are related to the duration of the disease.

Although some patients respond better to one antimalarial drug than to others (Cornbleet, 1956 ; Pappenfort, 1956), most cases are equally well controlled by any of them. Above a certain level, increased dosage produces no greater benefit (Christiansen and Nielsen, 1956). There remains, however, a hard core of about 20% of cases in which some activity persists. Systemic corticosteroids can be used in this group of cases, but in view of their undesirable side effects and the relatively benign nature of chronic L.E., they have not been widely employed. It would seem reasonable to use a combination of anti-malarial and corticosteroid drugs in this 20% if control can be obtained with a smaller dose of steroid than if the latter were given alone. Midana and Depaoli (1957) treated eighteen unselected cases of chronic L.E. with a combination of chloroquine and prednisone and found a quicker response than with chloroquine alone. The mixture was particularly useful when the scalp and extremities were involved.

INVESTIGATION.

Between 1955 and 1960, 62 patients with chronic L.E. were kept under observation in the Dermatological Department of the United Oxford Hospitals. Initially, they were all treated with mepacrine, chloroquine, or plaquenil (hydroxychloroquine) in the usual dosage for this condition, and in some cases the drug was subsequently stopped. One patient received camoquin (amodiaquin) which had been started in another clinic. Chloroquine and latterly plaquenil have replaced mepacrine. Several patients were given different members of this group of drugs in turn, particularly if treatment was unsuccessful with one or other. There remained a group of 15 patients in whom some degree of activity persisted ; all of these were treated with systemic corticosteroids in addition to the antimalarial drugs. Triamcinolone and latterly prednisolone have been used, the usual initial daily doses being 12-16 mg. and 15-20 mg. respectively, which were reduced to maintenance levels when activity ceased. Recently, prednisolone has been substituted for triamcinolone in most cases.

RESULTS.

The results are shown in Tables I and II. All eleven patients treated with

TABLE I.—*Analysis of Cases.*

	Male.	Female.
Number of cases	28	34
Age ranges (yrs.)	18-69	11-72
Mean age (yrs.)	44.3	42.2
Mepacrine	2	3
Chloroquine	24	31
Plaquenil	4	8
Camoquin	1	0
Controlled by antimalarials alone	19	28
Not controlled by antimalarials alone	9	6
Treated with combination	6	5
Controlled by combination	6	5

a combination of antimalarials and corticosteroids responded well and activity had usually disappeared within a month of starting combined therapy. Corticosteroids have been stopped in two patients with no relapse after three and eighteen months respectively. It has been found that the dose of corticosteroid

TABLE II.—*Summary of Patients Receiving both Antimalarials and Corticosteroids.*

Case.	Sex.	Age (yrs.).	Corticosteroid.	Present daily dose (mg.).	Duration of combined therapy (months).	Side effects.
1	M.	54	Triamcinolone	8	27	Control of coexistent psoriasis.
2	"	35	"	10	26	Nil.
3	"	52	Prednisolone Triamcinolone Prednisolone	Nil	10	Bilateral thrombophlebitis. Bilateral rupture of tendo achillis.
4	F.	37	Triamcinolone	4	22	Lassitude and weakness.
5	M.	40	"	Nil	3	Thrombophlebitis. Relapse of L.E. on stopping steroid.
6	F	30	" Prednisolone	15	14	Nil.
7	"	27	"	5	12	"
8	M.	30	Triamcinolone	Nil	9	"
9	F.	79	"	12	2	"
10	M.	43	Prednisolone	10	1	"
11	F.	57	"	15	1	"

could be reduced to maintenance levels of 4 to 8 mg. triamcinolone and 5 to 10 mg. prednisolone in most cases. Further reduction, however, failed to control the disease. Several fairly high doses of corticosteroids shown in Table II are due to the recent commencement of combined therapy in these patients. Side effects were experienced by three patients on triamcinolone after periods varying from three to six months. These were weakness and lassitude in a woman on 4 mg. triamcinolone daily, and thrombophlebitis in two men receiving 8 and 12 mg. triamcinolone daily respectively. One of these men subsequently developed simultaneous bilateral rupture of the tendo achillis; this was repaired surgically and the corticosteroid stopped: he has since remained well for eighteen months. Coexistent psoriasis was controlled in one patient.

SUMMARY.

Eleven patients with chronic discoid lupus erythematosus which had not responded satisfactorily to prolonged treatment with antimalarial drugs were given corticosteroids in addition, with complete control in every case.

Serious side effects were encountered in only one patient.

This combination is recommended for resistant cases.

We wish to thank Dr. H. R. Vickers for his help and encouragement in writing this paper.

REFERENCES.

- CHRISTIANSEN, J. V. and NIELSEN, J. P. (1956) *Brit. J. Derm.*, **68**, 73.
 CORNBLEET, T. (1956) *Arch. Derm., Chicago*, **73**, 572.
 GOLD, S. (1960) *Brit. J. Derm.*, **72**, 231.
 MIDANA, A. and DEPAOLI, M. (1957) *Dermatologica, Basel*, **115**, 677.
 PAGE, F. (1951) *Lancet*, ii, 755.
 PAPPENFORT, R. B. (1956) *Arch. Derm., Chicago*, **74**, 384.
 PROKOPTCHOUK, A. J. (1940) *Vestn. Vener. Derm.*, 2/3, cit. *Zbl. Haut.-u. GeschlKr.*, **66**, 112.

TOLBUTAMIDE IN THE TREATMENT OF SKIN DISEASES.

INDER SINGH, M.B.(Rangoon), F.R.C.P.E., F.R.F.P.S.

Professor of Medicine,

M. L. GAIND, M.B.(Punjab),

Adviser in Dermatology,

AND

D. JAYRAM, M.B.(Madras),

Specialist in Dermatology,

Armed Forces Medical College, Poona, India.

It is striking that patients treated with tolbutamide keep a remarkably clear scalp and are practically free from skin complications. We were, therefore, encouraged to use this drug in the treatment of the skin when in December, 1957, a six year old child, long afflicted with seborrhoeic dermatitis cleared completely with tolbutamide in barely twelve days. Since then we have treated several skin diseases and find that tolbutamide has a definite place in the treatment of seborrhoeic conditions, and that it may greatly benefit cases of psoriasis, acne vulgaris and dermatitis herpetiformis, and halt the progress of vitiligo. In many instances it has been possible to dispense with local treatment and in others recovery with existing methods was appreciably hastened. During the course of our work we have read with interest similar findings reported in psoriasis by Kabelitz and Kappel (1958) and in acne vulgaris by Cohen and Cohen (1959) and Bettley (1961).

INVESTIGATION.

Forty-four cases of dandruff, 35 cases of seborrhoeic dermatitis, 26 of adolescent acne vulgaris, 7 of prepubertal acne, 42 of psoriasis, 1 of pityriasis lichenoides, 4 of dermatitis herpetiformis, 6 of eczema, 18 of chronic dermatitis of legs, 7 of vitiligo, 9 of pityriasis alba, and 1 of pemphigus were treated with tolbutamide. All in-patients were seen daily and out-patients twice a week. The drug was given orally, 0.5 to 1.5 g. daily, with meals. No local or general treatment of any kind, unless otherwise stated, was given. We also tested the effect of combined tolbutamide and local therapy against placebo controls in psoriasis. Routine urine and blood examinations were made as required to exclude frank or latent diabetes mellitus before treatment and to record any lowering of existing blood sugar levels during it.

RESULTS.

I. *Seborrhoeic dermatoses*.—(i) *Dandruff*.—The scalp cleared completely within 7 to 18 days in 43 out of 44 cases (97.7%) and remained free of dandruff as long as the drug was administered. The remaining case was only partially

benefitted. He was, however, very responsive to local treatment and easily relieved with an anti-dandruff lotion in 5 days. The natural tendency for recurrence was apparently not abolished. At the earliest the scales reappeared 16 days after the withdrawal of treatment and 23 cases (52.3%) had full-fledged dandruff again within six months.

(ii) *Seborrhoeic dermatitis*.—Uniform improvement was noticed in 33 out of 35 cases (94.3%) in 8 to 10 days. Both dandruff and rash subsided within 4 to 6 weeks. On cessation of treatment dandruff showed a tendency to recur as in the uncomplicated cases of the condition. Rashes, however, did not appear in any case during the course of at least 12 months' follow-up. The remaining 2 cases (5.7%) were of seborrhoeic eczema with exudation and failed to respond. Tolbutamide itself did not appear to have affected them adversely as with adjuvant local therapy they both cleared up in 5 to 6 weeks.

(iii) *Seborrhoeic sycosis*.—A very resistant case showed improvement after 7 days of tolbutamide therapy and was completely cured within a fortnight. There was no recurrence for 3 months. Subsequently the individual did not report for a check, but we understand he has been free from skin trouble for more than a year.

(iv) *Acne vulgaris*.—The response to tolbutamide treatment was variable. Five out of 26 cases (19.2%) of resistant widespread pustular adolescent acne cleared up in about 8 weeks with only residual scarring. Seventeen cases (65.4%) showed moderate improvement. In them few old lesions disappeared and no fresh lesion were noticed. Four cases (15.4%), however, showed no response of any kind. Prepubertal acne was not affected and ran its natural course.

II. *Psoriasis*.—Uniform and steady initial improvement up to a stage occurred in 30 out of 32 cases (93.7%) treated with tolbutamide alone. Two cases, however, did not show any noteworthy change and were almost complete failures. In the former, erythema started disappearing in 8 to 10 days and after 3 to 4 weeks the scales peeled off very easily. Erythema was finally imperceptible in 4 to 6 weeks. Twenty-five of these 30 cases (78.1%) became static at this stage and showed no further improvement. Subsequent combined treatment with tolbutamide, tar and ultra-violet rays cleared their lesions in 1 to 4 weeks. In 3 cases (9.3%) with widespread lesions there was almost complete cure with tolbutamide alone. A few lesions which persisted on the extensor surface of the legs were abolished within a week with tar and ultra-violet rays. The lesions on the scalp, front of the chest, centre of the back and the groins, i.e., the seborrhoeic areas, were the first to disappear. It was interesting to note that the remaining 2 cases (6.3%) who had flexural psoriasis cleared up completely with tolbutamide without any adjuvant treatment.

Ten cases treated with tolbutamide, tar and ultra-violet rays from the very start cleared up in 2 to 4 weeks against the 5 to 8 weeks taken by 10 clinically

almost identical cases treated with placebo, tar and ultra-violet rays. The duration of treatment was, therefore, significantly reduced by the concomitant use of tolbutamide with local therapy.

III. *Pityriasis lichenoides*.—A case of pityriasis lichenoides varioliformis acuta, which had resisted every form of treatment for 4 months, showed dramatic response to tolbutamide on the fourth day and was cured in 2 weeks.

IV. *Dermatitis herpetiformis*.—In all 4 cases, which included 1 of the juvenile type, itching subsided within 5 days of tolbutamide treatment and the vesicular eruption cleared up in 8 to 10 days. In 3 of them (75%) no recurrence occurred during 10 months' follow up. The fourth case, however, recurred immediately after cessation of tolbutamide treatment and the second attack did not respond to the drug. With dapsone, however, he cleared up within 10 days but required subsequent maintenance treatment to remain free.

V. *Chronic dermatitis of legs*.—Pustular lesions cleared up completely in all the 18 cases in 2 to 4 weeks. Thickened eczematous areas and lichenified plaques, however, were unaffected even with prolonged treatment and required local x-ray therapy for their eradication.

VI. *Vitiligo*.—In 4 cases with very active disease no new lesions have appeared and existing lesions have not spread while on tolbutamide therapy for the past 16 to 37 months. In these and the remaining 3 cases who were more or less static, after about 3 weeks treatment with tolbutamide there was repigmentation of lesions at the margins, and in addition, several islands of pigmentation round hair follicles, more near the margins than elsewhere, were seen. The newly pigmented areas were, however, darker than the normal skin and were, therefore, rather unsightly. The unaffected pale areas looked flushed. The effects wore off gradually in 6 to 10 weeks when the drug was withdrawn.

VII. *Pityriasis alba*.—In contrast with tolbutamide therapy the palest areas in all the 9 cases of pityriasis alba disappeared completely within a month and the pigmentation was normal.

Eczema and pemphigus were neither benefitted nor adversely affected by tolbutamide.

The drug was tolerated well. Only one patient complained of headache and dizziness of hypoglycaemic origin each time the drug was administered. The symptoms were relieved with sugar and were temporary for a few days only. There were no allergic skin reactions in any case.

DISCUSSION.

None of these skin cases suffered from frank or latent diabetes mellitus. Also, significant lowering of blood sugar was recorded in only one case during tolbutamide therapy. The beneficial effect of the drug could not therefore be ascribed to its hypoglycaemic effect. Neumann (1958), however, recorded an average decrease of 27.4 mg. % in the skin sugar levels of eight out of nine

carbutamide-treated patients with psoriasis, who were not diabetics and in all of whom the skin sugar before therapy was raised. According to our preliminary findings, tolbutamide appears to have a similar effect on skin sugar levels as carbutamide. We, however, do not know the role of high skin sugar levels in psoriasis, but furunculosis, sweat gland abscesses, pruritus and resistance to therapy have long been thought to be associated with "skin diabetes" (Urbach and Le Winn, 1956). The benefit in acne vulgaris and pustular dermatitis may be due to the depression of skin sugar levels by tolbutamide, as a result of which the metabolism of associated infecting organisms is upset and their depredations accordingly abated or ended. The pityrosporon is possibly affected in the same way in seborrhoeic conditions.

Bocobo *et al.* (1952) have shown that the skin contains the same amino acids as other tissues, but with the exception of glycine, in lesser amounts. In experiments with rats, Sheffner and Bergeim (1954) concluded that a single amino acid may influence the rate at which other amino acids are utilized, and Elvehjem (1956) reported that this may even extend to true metabolic antagonism between two amino acids. As some of the amino acids appear to be related to the keratinization process, it is possible that tolbutamide may restore the disturbed keratinization in seborrhoeic conditions and psoriasis by aiding the synthesis of certain amino acids in the skin. It is known that it does so in other tissues. Thus, pretreatment of rats with tolbutamide has been observed by Recant and Fischer (1957) to accelerate the incorporation of C^{14} -glycine into protein in liver slices, and tolbutamide injected intravenously has been reported by DeMeutter *et al.* (1958) to decrease the serum alpha-amino acids in human subjects. These findings may well explain the benefit in psoriasis reported by Rowe (1960) with the use of alpha-amino acids *isoleucine*, *serine* and *methionine*. The drug also appears to influence the metabolism of *tyrosine* in vitiligo and pityriasis alba but the return of skin pigment in the former, due to factors at present undetermined, is patchy and unbalanced.

In psoriatic lesions, according to Lawler and Vineyard (1960), the capillaries are markedly elongated and tortuous but there is only minimal capillary dilatation. As the change persists after successful treatment it may have something to do with recurrences. Tolbutamide dilates the skin capillaries as is indicated by the flush in vitiligo (*vide supra*), but it is difficult for us at present to say to what extent this happens in psoriasis. It is, however, interesting to note that these vascular abnormalities are least marked in flexures, and it is in flexural psoriasis that we have found the action of tolbutamide to be the best. The lack of total response to tolbutamide seen in other cases may also be due to ineffective concentrations of tolbutamide obtained in the skin, inadequacy of required alpha-amino acids, or both factors. Work on these lines is in progress.

Another aspect of tolbutamide therapy which requires consideration is its

effect on sweating. Many patients felt that they sweated less and their skin and scalps were less greasy than before and we agreed with them. While this may have benefitted seborrhoeic conditions, it may on the other hand have been the cause of restricted response in psoriasis.

Finally, the buoyant effect of the drug probably had its own part to play. Some very remarkable responses were seen in local hyperidrosis of hands. Within a week of taking 1.5 g. tolbutamide daily, for example, one of our patients, a nervous employee, turned up happily to say he had hardly any sweating and he could now face his boss with confidence.

CONCLUSIONS.

Most seborrhoeic conditions can be completely cleared with tolbutamide without adjuvant local therapy. Although, there is lack of total response in most cases of psoriasis and acne vulgaris, tolbutamide accelerates healing and is the single most useful aid to local therapy. It is as effective as dapsone in the treatment of dermatitis herpetiformis. The progress of vitiligo is halted and there is an attempt at repigmentation. Pityriasis alba is cured. In chronic pustular dermatitis, eczematous and lichenified lesions do not heal. The drug is also ineffective in eczema and pemphigus.

We are grateful to Mr. G. Winternitz, Hoechst Pharmaceuticals, for supplies of Rastinon, and to Major-General C. C. Kapila, Commandant, Armed Forces Medical College, Poona, for permission to publish this paper.

REFERENCES.

- BETTLEY, F. R. (1961) *Brit. J. Derm.*, **73**, 149.
BOCOBO, D. L., SKELLENGER, M., SHAW, C. R. and STEELE, B. F. (1952) *Arch. Biochem.*, **40**, 448.
COHEN, J. L. and COHEN, A. D. (1959) *Canad. med. Ass. J.*, **80**, 629.
DEMEUTTER, R. C., KHACHADURIAN, A. K. and MARBLE, A. (1958) *Proc. Soc. exp. Biol. N.Y.*, **99**, 33.
ELVEHJEM, C. A. (1956) *Some Aspects of Amino Acid Supplementation*. New Brunswick, N.J.: Rutgers University Press.
KABELITZ, G. and KAPPEL, W. (1958) *Dtsch. med. Wschr.*, **27**, 1167.
LAWLER, J. C. and VINEYARD, W. R. (1960) *Arch. Derm., Chicago*, **82**, 190.
NEUMANN, E. (1958) *Dermatologica, Basel*, **117**, 172.
RECANT, L. and FISCHER, G. L. (1957) *Ann. N.Y. Acad. Sci.*, **71**, 62.
ROWE, L. (1960) *Arch. Derm., Chicago*, **81**, 405.
SHEFFNER, A. L. and BERGEIM, O. (1954) *Arch. Biochem.*, **49**, 327.
UBBACH, E. and LE WINN, E. B. (1946) *Skin Diseases, Nutrition and Metabolism*. New York: Grune and Stratton.
-

THE TREATMENT OF ACNE VULGARIS WITH DAPSONE

CYRIL M. ROSS, M.B., Ch.B., M.R.C.P., F.R.F.P.S.

Dermatologist to the Boksburg-Benoni and Far East Rand Hospitals.
Address : 303 Medical Centre, Pretorius St., Pretoria, South Africa.

ANTIBIOTICS have been recommended in the treatment of acne vulgaris but they are expensive and may have disagreeable side effects. For this reason, a cheap and safe alternative has been sought, and it has been found that dapsone has a beneficial effect on a significant percentage of cases of acne.

Dapsone (DADPS, di, 4-aminophenyl sulphone) was first synthesized in 1908. It has antibacterial activity against a wide range of organisms including *Mycobacterium leprae*, *Mycobacterium tuberculosis*, streptococci and pneumococci and has been used extensively in the treatment of leprosy and dermatitis herpetiformis. Its pharmacological action is similar to that of the sulphonamides and it functions as a bacteriostatic by preventing the use by organisms of certain metabolites essential to their development. It is not free from side effects and it is certainly not a drug to be administered casually to any patient who cannot be kept under close observation. To avoid serious reactions the blood level of the drug should never be allowed to exceed 1 mg. per 100 ml. The dose should begin at 50 mg. per diem and should only be increased when the absence of side effects has been confirmed after seven days at that level. Subsequent increases to 100 mg. and then to 150 mg. per diem may then be made if necessary, but 200 mg. a day should never be exceeded. When given by mouth, the drug is well absorbed and, because of slow excretion, blood levels are well maintained. Less than 5% is passed in the faeces and the remainder is found in the urine. With ordinary doses, measureable levels persist in the blood for 15 days and traces are found much later. Headache, which is the commonest side effect, may be accompanied by cyanosis of the lips and is due to methaemoglobinaemia. The other toxic effects resemble those seen with many other drugs and are not easily explained on a basis of any specific physiological upset. While I have not come across any reports of a harmful effect on the white cells, others have noted instances of hypochromic and haemolytic anaemia and I have seen the latter when using the drug for dermatitis herpetiformis. In the present trial, headache, listlessness, dizziness, epistaxis, general malaise and a maculopapular rash were observed. In no instance, however, did the side effects produce much distress and they never persisted when the drug was discontinued. It is nevertheless clearly a drug to be used with care.

INVESTIGATION.

A double-blind trial was conducted with 46 patients aged 12 to 26. Active and placebo tablets were identical in appearance and were identifiable only by code numbers on the outer wrapper of their containers. Alternate patients were treated with each preparation, the selection depending solely on the order in which they presented themselves. There was no allocation to one or other group on a basis of age, sex, severity, duration or type of case. The patients were informed that the purpose of the tablets was "to control infection in their spots." No comment was made on their efficacy but the patients were told that side effects were possible and they were asked to report them. As a rule, patients were seen at intervals of seven days during the first two weeks and thereafter as required by their progress. They received in addition, such local and general treatment as seemed appropriate to their case. They were all seen in private practice.

RESULTS.

The preparations used were identified by the code numbers 704 and 705. Tablet 704 was revealed at the end of the trial to be dapsone: 705 was the placebo. Forty-six patients were treated, 23 with dapsone and 23 with the placebo. Nine of those on dapsone were greatly improved and 3 were improved: 9 showed no improvement and 2 defaulted. With the placebo, 3 were greatly improved, 2 improved and 18 showed no improvement. Six of those on dapsone and 3 on the placebo developed side effects (Table I). Taking the figures as

TABLE I.—*Overall Results of Treatment.*

Treatment.	Total.	Number of patients.				
		Greatly improved.	Improved.	Not improved.	Defaulted.	Side effects.
Dapsone (704) .	23	9	3	9	2	10 (in 6 patients)
Placebo (705) .	23	3	2	18	0	3

they stand and applying the conventional statistical test, the higher frequency of side effects and the higher frequency of improved and greatly improved cases with dapsone compared with the placebo are statistically significant at the 5% level.

TABLE II.—*Severity and Sex.*

	Males.			Females.			Total.	
	Mild.	Moderate.	Severe.	Mild.	Moderate.	Severe.	Males.	Females.
Dapsone (704) .	2	6	4	4	2	3	12	9
Placebo (705) .	1	2	4	4	11	1	7	16

The distribution of the severity of acne in the two groups is shown in Table II. It is clear that the groups treated with tablets 704 and 705 were not well balanced with respect to the severity of the complaint and it would obviously

have been more satisfactory had they been so. However, there does not appear to be any correlation between the initial severity and the degree of improvement noted, so that the difference in the distribution is of less consequence.

TABLE III.—*Response by Sex.*

Treatment	Males.			Females.		
	Greatly improved.	Improved.	No improvement.	Greatly improved.	Improved.	No improvement.
Dapsone (704) .	4	1	7	5	2	2
Placebo (705) .	2	1	4	1	1	14

The response according to sex is displayed in Table III. Combining the first two groups, we obtain the results shown in Table IV. Dapsone as compared with the placebo produced no apparently greater degree of im-

TABLE IV.—*Response (Simplified).*

Treatment	Males.			Females.		
	Improved.	Not improved.	Total.	Improved.	Not improved.	Total.
Dapsone (704) .	5 (42 %)	7 (58 %)	12	7 (78 %)	2 (22 %)	9
Placebo (705) .	3 (43 %)	4 (57 %)	7	2 (13 %)	14 (87 %)	16

provement in males but a statistically highly significant improvement in females ($P < 0.01$). The apparent differential action in males and females is just sufficient to be regarded as statistically important but this finding needs further support before it can be regarded as definite.

The numbers of patients out of the total in each group showing side effects

TABLE V.—*Incidence of Side Effects.*

Treatment.	Males.	Females.
Dapsone (704) .	2/12	4/9
Placebo (705) .	3/7	0/16

are shown in Table V. There is an apparent marked increase in the proportion of females showing side effects, but considering the smallness of the groups, this increase is not quite statistically significant ($P = 0.10$).

DISCUSSION.

When these results are compared with the results achieved in the many series of cases treated with antibiotics, it is apparent that these broad-spectrum drugs are more effective than dapsone. Against this superiority, however, one

must offset not only the great saving in expense, but the absence of certain toxic reactions which are common to the antibiotics and the freedom from any risk that resistant strains of organisms will develop. There were no cases of glossitis, vomiting, pruritus ani or enterocolitis. Dapsone therefore merits consideration in the treatment of acne.

SUMMARY.

The results of treatment of a series of 46 successive cases of acne vulgaris, 23 of which were treated with dapsone and 23 with a placebo, are analysed statistically.

The investigation was carried out as a double-blind trial and shows that, at the 5% level, a statistically significant number of cases respond favourably to the administration of dapsone.

I wish to thank Imperial Chemical Industries Ltd. for supplies of dapsone and placebo tablets, and Dr. O. L. Davies, of Imperial Chemical Industries, Pharmaceuticals Division, Manchester, for assistance with the statistical analysis.

SUBSTITUTION OF ZINC OXIDE BY TITANIUM DIOXIDE IN SALICYLIC ACID PASTES.

H. R. DE VRIES.

The Dermatological Department, Municipal Hospitals, The Hague, Holland.
Chief : Dr. M. K. Polano.

LASSAR'S paste has been employed extensively in dermatological practice and most dermatologists have thought that they obtained the effects of salicylic acid by using it. Young and Weiffenbach (1959), however, demonstrated that the salicylic acid and zinc oxide in Lassar's paste reacted to form zinc salicylate : even in a freshly prepared sample, no free salicylic acid was found. The addition of salicylic acid to bases containing zinc oxide seems irrational, as the therapeutic action of zinc salicylate is similar to that of zinc oxide. Yet we may want to employ the actions of salicylic acid, the keratolytic one especially, through the use of a paste.

Therefore we searched for a substitute for zinc oxide in our salicylic acid pastes. According to Czetsch-Lindenwald and Schmidt La Baume (1950), *Martindale* (1958) and Osol and Farrar (1955), titanium dioxide seemed to be suitable. It is a white, amorphous, tasteless and odourless powder. It is chemically more inert than zinc oxide and some of its pharmaceutical properties are superior to those of the latter. It is regarded as non-toxic ; it is allowed for instance to be used as a covering paint in foods in Holland and other countries. It is added to several cosmetic preparations and also to a number of proprietary creams and pastes. Titanium dioxide is available in a technical and a purified quality. While the purified quality cannot be dispensed with for internal use as an absorbent in the intestines, its high price would make it more or less prohibitive for regular external use. Crude titanium dioxide, however, is suitable for external application as was proved by Steiger and Beuttner (1956). The price of this quality is only twice that of zinc oxide. We carried out a series of experiments in order to find out whether titanium dioxide was suitable for our purpose. First we tried to determine whether titanium dioxide reacted with salicylic acid in a paste. Second we examined the effect of salicylic acid on the skin in a base containing titanium dioxide.

INVESTIGATIONS.

Our first experiments were based upon a phenomenon described by Siemens and Schreiber (1946) who found that ammoniated mercury and salicylic acid, when applied together in ointments on the skin, could irritate, because they reacted with each other to form a quantity of mercuric chloride. Young found that if ammoniated

mercury and salicylic acid were brought together in a base containing zinc oxide, this toxic effect did not occur. He concluded that no free salicylic acid was present.

Starting from this principle, we mixed a number of ointments and pastes and with these we performed patch tests on the skin of healthy individuals. The composition of the preparations is listed below.

1. Ammoniated mercury	10	4. Ammoniated mercury	10
Salicylic acid	2	Salicylic acid	2
White soft paraffin	to 100	Crude titanium dioxide	—
		Potato starch aa	to 45
		Arachis oil	10
		White soft paraffin	to 100
2. Ammoniated mercury	10	5. Ammoniated mercury	10
Salicylic acid	2	Crude titanium dioxide	—
Zinc oxide	10	Potato starch aa	to 45
White soft paraffin	to 100	Arachis oil	10
		White soft paraffin	to 100
3. Ammoniated mercury	10	6. Crude titanium dioxide	—
Salicylic acid	2	Potato starch aa	to 45
Crude titanium dioxide	10	Arachis oil	10
White soft paraffin	to 100	White soft paraffin	to 100

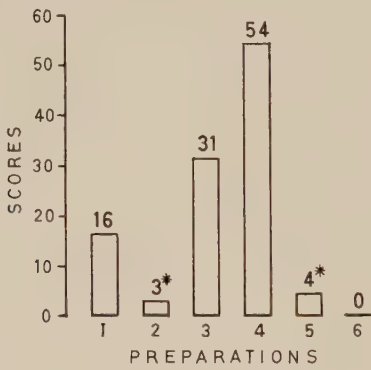


FIG. 1.

These were carried out by applying the preparations on a piece of lint one square centimetre in size under adhesive tape. For each person we chose a different sequence when applying the various preparations ; in this way we obtained blind readings of the effect. All readings were performed by the same physician 48 and 72 hours after application. The reactions were evaluated and recorded with numbers from 0 to 5 according to their intensity.

RESULTS.

In Fig. 1 the total scores in 22 test persons are given. The columns marked with an asterisk represent results due to allergy to mercury, subsequently confirmed. From this first series the following conclusions may be drawn.

(i) In accordance with Young's findings, we found preparations containing zinc oxide, salicylic acid and ammoniated mercury had no mercuric chloride effect. No free salicylic acid seemed to be present in a base containing zinc oxide (Fig. 1, column 2).

(ii) With 10% titanium dioxide in soft paraffin, a stronger mercuric chloride effect was seen than when soft paraffin alone is used as a base (Fig. 1, compare columns 1 and 3).

(iii) This toxic mercuric chloride effect became still stronger when a titanium dioxide paste rather than an ointment was used as a base (Fig. 1, column 4).

(iv) Titanium dioxide alone in a paste gave no reaction (Fig. 1, column 6).

The assumption that salicylic acid in bases containing titanium dioxide may exert its normal salicylic acid effect now seemed to be justified.

INVESTIGATION.

To substantiate this, we carried out a new series of patch tests with the pastes listed below.

7. Salicylic acid 10	14. Salicylic acid 20
Zinc oxide —	Crude titanium dioxide —
Potato starch aa to 45	Potato starch aa to 45
Arachis oil 10	Arachis oil 10
White soft paraffin . . . to 100	White soft paraffin . . . to 100
8. Salicylic acid 20	15. Salicylic acid 20
Zinc oxide —	Crude titanium dioxide . . to 45
Potato starch aa to 45	Arachis oil 10
Arachis oil 10	White soft paraffin . . . to 100
White soft paraffin . . . to 100	
9. Salicylic acid 20	16. Resorcin 10
Zinc oxide to 45	Crude titanium dioxide —
Arachis oil 10	Potato starch aa to 45
White soft paraffin . . . to 100	Arachis oil 10
	White soft paraffin . . . to 100
10. Resorcin 10	17. Resorcin 20
Zinc oxide —	Crude titanium dioxide —
Potato starch aa to 45	Potato starch aa to 45
Arachis oil 10	Arachis oil 10
White soft paraffin . . . to 100	White soft paraffin . . . to 100
11. Resorcin 20	18. Salicylic acid 10
Zinc oxide —	Resorcin 10
Potato starch aa to 45	Crude titanium dioxide —
Arachis oil 10	Potato starch aa to 45
White soft paraffin . . . to 100	Arachis oil 10
	White soft paraffin . . . to 100
12. Salicylic acid 10	19. Lanette Wax N 10
Resorcin 10	Arachis oil 10
Zinc oxide —	Water to 80
Potato starch aa to 45	After making a cream, add—
Arachis oil 10	Salicylic acid 10
White soft paraffin . . . to 100	Resorcin 10
13. Salicylic acid 10	20. Salicylic acid 20
Crude titanium dioxide —	White soft paraffin . . . to 100
Potato starch aa to 45	
Arachis oil 10	
White soft paraffin . . . to 100	

These pastes were applied as before. The irritation caused by the pastes was again rated with numbers from 0 to 5.

With this experiment our intention was to evaluate and compare the irritating effect of salicylic acid in pastes containing zinc oxide and crude titanium dioxide.

At the same time we wanted to compare this with the effect of resorcin and the combination of salicylic acid and resorcin, because in our routine treatment of acne vulgaris this combination is applied frequently with apparent success.

RESULTS.

In Fig. 2 the total scores on 24 persons tested are given. The salicylic acid in zinc paste had no visible effect, as was to be expected. The irritating effect of salicylic acid in the titanium dioxide paste was greater than in the white soft paraffin. Substitution of a part of the titanium dioxide by potato starch

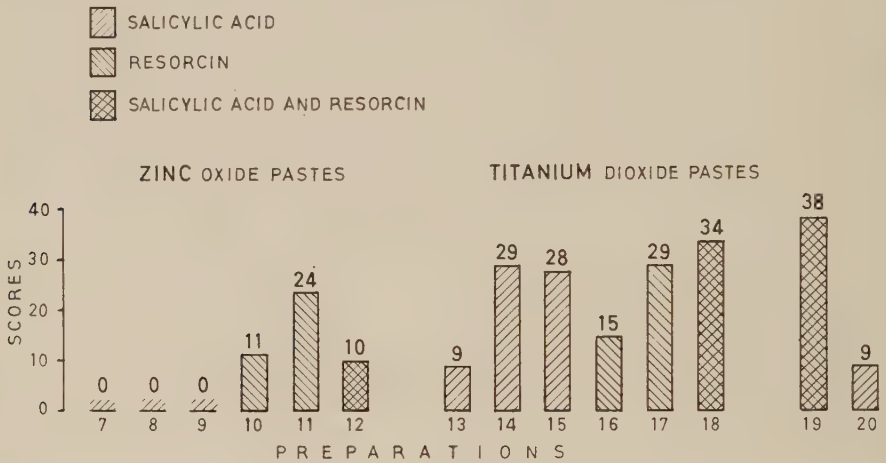


FIG. 2.

seemed to have no influence on the effect of the salicylic acid. Resorcin brought about the same degree of irritation in zinc oxide and in titanium dioxide pastes. Combination of 10% salicyclic acid and 10% resorcin caused an irritation comparable with that of 20% of these substances alone. Application of these substances in a O/W cream caused very strong irritation.

It seems on the grounds of these experimental results that in crude titanium dioxide we have a suitable ingredient for the compounding of pastes in which salicyclic acid is effective on the skin. Therefore, if the local application of salicyclic acid is indicated, it seems rational to substitute crude titanium dioxide for zinc oxide in our prescriptions.

The following are the formulae of two examples ; one of a greasy and the other of a drying paste.

Salicylic acid	2-20
Crude titanium dioxide	—
Potato starch aa	to 45
Arachis oil	10
White soft paraffin	to 100

Bentonite	4
Salicylic acid	2-30
Crude titanium dioxide	—
Talcum aa	to 30-50
Glycerin	—
Water aa	to 100

These have now been prescribed in our department for a year in the treatment of several skin conditions in which the keratolytic effect of salicylic acid was desired, e.g. eczemas with hyperkeratosis and acne vulgaris. A further advantage of the drying paste is that it keeps well even if high concentrations of salicylic acid and resorcin are added, compared with drying pastes containing zinc oxide which become very dry and stiff after some time. After three months, a titanium dioxide drying paste with salicylic acid and resorcin showed the same properties as a freshly prepared one.

SUMMARY.

The use of salicylic acid in zinc pastes is irrational because salicylic acid combines with zinc oxide to form zinc salicylate which has the same properties as zinc oxide.

The presence of free salicylic acid in pastes containing crude titanium dioxide could be substantiated by patch tests on healthy individuals. In a second series of patch tests with analogous zinc and titanium pastes, the irritating effects of salicylic acid, resorcin and the combination of salicylic acid and resorcin were compared.

Titanium dioxide is a suitable substitute for zinc oxide in pastes containing salicylic acid.

REFERENCES.

- CZETSCH-LINDENWALD, H. VON and SCHMIDT LA BAUME, F. (1950) *Salben, Puder, Externa* 3rd edn. Berlin : Springer.
- OSOL, A. and FARRAR, G. E. (1955) *The Dispensatory of the U.S.A.*, 25th edn. Philadelphia : Lippincott.
- POLANO, M. K. (1952) *Skin Therapeutics*. Amsterdam : Elsevier.
- SIEMENS, H. W. and SCHREIBER, O. (1946) *Dermatologica, Basel*, **93**, 89.
- STEIGER, K. and BEUTTNER, W. (1956) *Schweiz. ApothZtg.*, **94**, 85.
- The Extra Pharmacopeia* (Martindale) 1958, 24th edn., Vol. 1. London : Pharmaceutical Press.
- YOUNG, E. and WEIFFENBACH, N. (1959) *Dermatologica, Basel*, **118**, 74.
-
-

A NEW OINTMENT BASE.

C. F. H. VICKERS, M.D., M.R.C.P.(LOND.), M.R.C.P.(ED.),

AND

I. B. SNEDDON, M.B., F.R.C.P.

The Rupert Hallam Department of Dermatology, Sheffield Royal Infirmary.

AFTER we had observed the beneficial effects of a proprietary "moisture" cream on the skin of members of our families, we decided to investigate the therapeutic properties of such creams when applied to ichthyotic skin; the therapy of ichthyosis is unsatisfactory and it was felt that this was a good condition on which to test their emollient properties. A preliminary short double-blind trial of a proprietary moisture cream and Ung. Aquosum B.P. showed the former to be superior and a further double-blind paired comparison was then undertaken to determine whether this superiority was due to the "moisturizing" constituent or to the base of the ointment.

INVESTIGATION.

Messrs. Boots kindly provided a cream base (E.45) such as is used in cosmetic moisture creams, although the original observations which drew our attention to these creams were not made on their products. The formula of this cream was :

	%
Stearic acid	3.3
Glyceryl monostearate, self-emulsifying, B.P.C.	6.2
Wool fat B.P.	1.0
White soft paraffin B.P.	14.3
Light liquid paraffin B.P.	11.4
Methyl hydroxybenzoate B.P.C.	0.1
Triethanolamine B.P.C.	1.4
Distilled water	62.3

Two ointments were used in the first trial, X being Boots cream E.45 plus 1% propylene glycol, one of the so-called moisturizing factors, and Y the cream E.45 alone. These were supplied in identical tubes and the patients were instructed to apply X to one side of the body and Y to the other. The sides were selected at random and subjective and objective observations were made at one, three, six, nine and twelve weeks, with a final assessment at six months.

Twenty-three patients suffering from ichthyosis vulgaris were admitted to this trial. A second trial of Y and ung aquosum B.P. was then undertaken under similar conditions and twenty-seven patients were admitted to this trial.

RESULTS.

In the first trial the patients preferred E.45 plus propylene glycol to E.45 alone. In the first six weeks it appeared to be superior objectively, but no difference could be detected between the two creams at the end of six months.

TABLE I.—*Results of Trials of X, Y, and Ung. aquosum B.P.*

Trial.		Improvement.			
		Subjective.		Objective.	
		At 6 weeks.	At 6 months.	At 6 weeks.	At 6 months.
1	$X > Y$	19	17	16	0
	$Y > X$	2	3	0	0
	$Y = X$	2	3	7	23
2	$Y > \text{Ung. aquosum}$	25	25	22	25
	$\text{Ung. aquosum} > Y$	0	0	0	0
	$\text{Ung. aquosum} = Y$	2	2	5	2

In the second trial E.45 was both subjectively and objectively superior at six weeks and six months in twenty-five of twenty-seven patients. In several cases where eczema was present together with ichthyosis, the cream was not well tolerated on the eczematous areas.

DISCUSSION.

We believe that cream E.45 is a useful new ointment base which is valuable in the treatment of ichthyosis. It is acceptable to the patient and relatively cheap to produce. As the treatment of ichthyosis is prolonged, these factors are important. Since the completion of the trial, the ointment has been used for patients with traumatic dermatitis, especially housewife's dermatitis, and several surgeons whose hands have become chapped after prolonged scrubbing up found it more acceptable and more effective than other preparations available in the pharmacopoeia. Another short trial with 1% salicyl acid in this base appeared to give extremely satisfactory results in ichthyosis but the mixture was unstable. Further work has shown that the base is compatible with hydrocortisone, ichthammol, solution of coal tar, resorcinol, sulphur, ammoniated mercury and calamine. The appearance of crude coal tar in the base is unsatisfactory.

SUMMARY.

A new ointment base is described which is useful in the treatment of ichthyosis. In addition, it would appear to be a satisfactory vehicle for a wide range of medicaments.

We wish to thank Dr. P. T. Main of Boots Pure Drug Co. Ltd. for considerable help and for the supply of materials for this study

EXOGENOUS OCHRONOSIS AND MYXOEDEMA FROM RESORCINOL.

A. E. THOMAS, B.Sc., M.B., CH.B., M.R.C.P.

Senior Medical Registrar, General Hospital, Nottingham,

AND

M. A. GISBURN, M.B., CH.B.

Registrar, Department of Dermatology, Nottingham.

THE term ochronosis was coined by Virchow (1866) to describe blackening of the cartilages in the body of a man of sixty-seven who had died from aneurysm. Its association with alkaptonuria was appreciated by Albrecht (1902) and Osler (1904); in 1906 Pope and Pick respectively described cases arising from prolonged external use of phenol. Patients with ochronosis fall into two main groups.

(i) Endogenous ochronosis which is associated with the passage of homogentisic acid in the urine as a result of an inborn error of metabolism.

(ii) Exogenous ochronosis in which homogentisic acid is absent from the urine but in which phenol or a related compound has been absorbed into the body over a prolonged period.

The clinical features of the condition were reviewed by Oppenheimer and Kline (1922) who drew attention to the associated degenerative arthritis and the high incidence of serious cardiovascular disease in recorded cases, whether endogenous or exogenous.

Bull and Fraser (1950) found excessive iodine uptake in the thyroid glands of three myxoedematous patients whose leg ulcers had been treated with ointment containing resorcinol, which they concluded was an antithyroid agent. Similar findings were noted by Hart and MacLagan (1951) and Hobson (1951). The association of exogenous ochronosis and myxoedema due to absorption of resorcinol from leg ulcers does not, however, appear to have been recorded.

CASE RECORD.

A housewife aged 59 attended as an out-patient and was later admitted to hospital complaining of loss of energy, ulceration of the legs and the passage of dark urine, the colour of which deepened on standing. The ulceration resulted from phlebitis thirty-three years previously. For thirteen years she had applied daily to these ulcers an ointment containing 12.5% resorcin and 12.5% glycerin in a soft paraffin base. Six years ago she developed a prolonged illness characterized by extreme loss

of energy and generalized oedema, which was diagnosed clinically as myxoedema; her symptoms were relieved by treatment with thyroid tablets. The ulceration had become so extensive in the last two years that she had recently been using as much as a pound and a half of ointment every ten days.

Examination.—She was a pale woman with a moderate goitre, who though still obese, showed signs of recent loss of weight. The mucous membranes were pale, the tongue smooth, red and sore and koilonychia was marked. A bluish-grey discoloration of the concha and antihelix gave her ears a dirty appearance, whilst triangular brown patches with their bases towards the cornea could be seen on the sclerotics (Fig. 1). Both lower legs showed ulcers extending around the full circumference from the ankles to the knees. A black deposit was present on the ulcers and the surrounding skin. There were signs of osteoarthritis of the knees.



FIG. 1.

Investigations.—Hb 8.7 g. 100 ml., M.C.H.C. 25%. W.B.C. 15,000 per cu. mm. (neutrophils 85%, lymphocytes 11%, monocytes 5%, eosinophils 1%). Blood Wassermann reaction negative. Faecal occult blood tests negative on three occasions. Blood urea 29 mg./100 ml.

Urine examined at a time when resorcin ointment was being applied did not contain homogentisic acid, but 2.1% of a mixture of resorcinol glucuronide and resorcinol monosulphate. The darkening on standing was considered to be due to oxidative polymerization of the resorcinol. Free resorcinol was not detected.

Progress.—A diagnosis was made of exogenous ochronosis and hypothyroidism induced by treatment with resorcinol. During her stay in hospital, the legs were prepared for skin grafting, but two months after admission, she developed acute abdominal pain with vomiting and died within a few hours.

Autopsy.—The immediate cause of death was an extensive mesenteric thrombosis with gangrene of three-quarters of the small intestine. The spleen contained a number of infarcts and the middle third of the aorta was the site of a very extensive mural thrombus. The thyroid gland was enlarged.

DISCUSSION.

The nature of the pigment in ochronosis is still undetermined. Virchow noted that it was taken up by the intercellular substance rather than by the cells and considered it was an organic pigment derived from haematin. Chemical studies led Pick to the conclusion that both endogenous and exogenous ochronosis were due to melanin formation. The more generally accepted explanation, however, was put forward by Albrecht (1902) and later by Garrod (1908), who considered the pigment to be an oxidation product of homogentisic acid in the case of endogenous ochronosis and of substituted phenols in exogenous ochronosis.

Attention has also been called to the frequent association of cardiovascular lesions with ochronosis and it has been suggested that these changes, like those in the joints, are dependent on the underlying metabolic disorder. Oppenheimer and Kline analysed a series of forty-one cases of both endogenous and exogenous ochronosis reported in the literature, comprising twenty-two females and nineteen males, with an average age of fifty-one years. Of these, nineteen came to autopsy and serious disease of the cardiovascular system—largely degenerative—was found in all, together with extensive pigmentation of the intima of the aorta and the endocardium. It is of some interest in the present case to speculate on the influence which the treatment of the leg ulcers with resorcin had on the severe atheroma of the aorta which was the eventual cause of death and which was also partly responsible for the final extent of the ulcers.

Resorcinol or dihydroxyphenol is unrelated chemically to any of the known groups of antithyroid drugs. Bull and Fraser consider that some of its chemical features may be relevant to its antithyroid action. It can be readily iodinated to form tri-iodoresorcinol and by competing with tyrosine for the iodinating mechanism in the thyroid gland, may block the formation of thyroid hormone.

Anaemia has been reported in a number of cases of chronic resorcinol intoxication. Resorcinol is known to produce methaemoglobinaemia and acute haemolytic anaemia has been a feature of the cases of acute poisoning reported in children (Cunningham, 1956). It would be reasonable, therefore, to suppose that the anaemia of chronic resorcinol poisoning was also due to increased haemolysis. In the present case, however, the anaemia was clearly due to iron deficiency. A further patient who had been applying resorcinol ointment to her leg ulcers has recently come to our notice. She presented with a normochromic anaemia of moderate severity (Hb 9 g./100 ml.). Survival studies using red cells labelled with ^{32}Cr have given normal values and do not suggest that increased haemolysis is the cause of her anaemia, which has improved spontaneously since she stopped using resorcinol.

SUMMARY

A case is reported in which ochronosis and myxoedema occurred together in a patient who had been applying resorcinol ointment to leg ulcers. The associated clinical features are discussed.

We are indebted to Dr. D. I. McCallum and Dr. J. D. Procter for advice, encouragement and access to patients under their care. To Dr. J. B. Foote we express our gratitude for the autopsy findings. Thanks are also due to the Medical Department of Messrs. Boots Limited for library facilities and to Mr. V. Osbourn, who assisted with translations.

REFERENCES

- ALBRECHT, H. (1902) *Z. Heilk.* **23**, 366.
BULL, G. M. and FRASER, R. (1950) *Lancet*, i, 851.
CUNNINGHAM, A. A. (1956) *Arch. Dis. Childh.*, **31**, 173.
GARROD, A. E. (1908) *Lancet*, ii, 73.
HART, F. D. and MACLAGAN, N. F. (1951) *Ibid.*, 530.
HOBSON, Q. J. G. (1951) *Proc. R. Soc. Med.*, **44**, 164.
OPPENHEIMER, B. S. and KLINE, B. S. (1922) *Arch. intern. Med.*, **29**, 732.
OSLER, W. (1904) *Lancet*, i, 10.
PICK, L. (1906) *Klin. Wschr.*, **43**, 478.
POPE, F. M. (1906) *Lancet*, i, 24.
VIRCHOW, V. R. (1866) *Virchow's Arch.*, **37**, 212.
-
-

BRITISH ASSOCIATION OF DERMATOLOGY

FORTY-FIRST ANNUAL MEETING.

THE Forty-first Annual Meeting of the Association was held in Liverpool on 6, 7 and 8 July, under the presidency of Dr. G. W. Bamber. It was attended by 79 members and 15 visitors. At the Business Meeting the following were elected to serve on the Executive Committee for 1961-62.

President :	Prof. G. H. Percival.
Immediate Past President and	
Assistant Editor :	Dr. G. W. Bamber.
Vice-President :	Dr. H. W. Gordon.
Hon. Treasurer :	Prof. J. T. Ingram.
Hon. Secretary :	Dr. D. I. Williams.
Hon. Editor :	Dr. P. J. Hare.

Ordinary Members of the Committee :

Dr. S. T. Anning.	Dr. H. J. Wallace.
Dr. J. M. Beare.	Dr. R. P. Warin.
Dr. G. B. Mitchell Heggs.	Dr. D. S. Wilkinson.
Dr. E. J. Moynahan.	Dr. H. T. H. Wilson.
Dr. J. R. Simpson.	

Dr. Norman Wrong (Toronto) was elected an Honorary Member and Prof. J. G. Orbaneja (Madrid) and Prof. J. Piérard (Ghent) Honorary Foreign Members.

The following were elected Ordinary Members :

Dr. I. W. Caldwell.	Dr. R. W. Riddell.
Dr. R. G. Howell.	Dr. P. F. D. Naylor.
Dr. I. A. Magnus.	Prof. H. V. Morgan.
Col. P. C. Mitchell, R.A.M.C.	S/Cdr. R. W. B. Scutt, R.N.

The first morning of scientific business was devoted to papers on genetics. Dr. C. A. Clarke spoke on the criteria for inherited factors in disease and selected for discussion the parent/offspring sib/sib correlation, associations with genetic markers and abnormalities of serum gammaglobulin. Dr. C. O. Carter followed with a paper on genetics in relation to dermatology. He showed how a knowledge of genetics was of value in advising parents and appealed to dermatologists to establish the normal variations of the structure and function of the skin. Dr. S. Walker then "called" the square dance of the genes which enabled one to see

how chromosomal aberrations arose: there was, however, no evidence to suggest that any congenital malformation of the skin was due to such *mesalliances*.

In the afternoon, Dr. I. Whimster spoke on freckles in Bantu albinos. He would be pleased to hear from anyone who knew of a Caucasian albino with freckles. A trio of papers on psoriasis excited much discussion. Most members seemed familiar with the clinical picture described by Dr. R. P. Warin as napkin psoriasis, but few appeared to accept that it was due to psoriasis. Dr. C. H. Whittle described the results of a double-blind sequential trial of an ointment containing vitamin A and triamcinolone in the treatment of psoriasis. Compared with triamcinolone ointment it produced statistically significant improvement, but relapse was frequent and the treatment was costly. Dr. F. F. Hellier showed that the great majority of cases of psoriasis could be cleared up in under three weeks by the Ingram method: his slides demonstrated not only spectacular involution of psoriasis but also indubitable change of sex in one instance. Dr. F. R. Bettley described his experiments with a perspex chamber designed to permit the study of the effects of soap on the permeability of isolated epidermis. Dr. Louis Winer of Los Angeles spoke on the pathological changes in cartilage in chondrodermatitis nodularis helcis, systemic chondritis and psoriatic arthropathy.

Friday morning provided a varied programme. Dr. H. K. King, deputizing for Prof. R. A. Morton, briefly reviewed the biochemistry of characteristic skin compounds such as keratin, melanin and lipids, and then discussed nutritional disorders, kwashiorkor especially. Dr. Honor Fell, in a speech of classical composure and clarity, described the effect on embryonic skin of growing it in abnormal sites or in media containing vitamin A or hydrocortisone. Apologizing needlessly for the academic nature of her theme, she hinted darkly that news of more practical application might soon be issued by her laboratory. Prof. A. W. Downie described the cutaneous manifestation of virus disease and the morning concluded with a clinical paper by Dr. T. Cochrane on diffuse alopecia in young women.

The clinical case meeting was held on Saturday morning. The out-patient department of Liverpool Royal Infirmary afforded so much space that it was possible for members to examine the seventy patients in less time than is required for quarter the number of cases in cramped accommodation. The ensuing discussion was conducted with equal expedition.

The social programme opened with a reception for members and guests given by the Lord Mayor of Liverpool. This was held in the Town Hall whose elegance recalled parts of Bath which was less surprising when it was learned that both were designed by John Wood. The president graciously entertained members and guests at the Landfall Club Ship moored in Canning Dock. Sea Scouts patrolling in a whaler were not called upon to exercise their skill in first

aid. Golf was played at the Royal Liverpool course at Hoylake when the Dowling-McCaw Cup was won by Dr. T. Cochrane for the second year in succession. Sailing at the West Kirby Sailing Club had unfortunately to be abandoned due to circumstances beyond the control of the sailors. Those with more discrimination than energy were taken on a coach tour of the city, visiting the awful caverns of the Cathedral and the priest holes of Speke Hall. The Annual Dinner was held at the Adelphi Hotel when the chief guests were the Lord Mayor and Lady Mayoress, Dr. and Mrs. R. Stopford-Taylor. Dr. H. J. Wallace welcomed the guests in a speech whose sparkling effervescence amused even the Toast Master; Dr. C. A. Clarke fittingly responded. Dr. R. M. B. McKenna, in reminiscent vein, proposed the health of the Association coupled with the name of the President.

The 1943 meeting which was to have been held in Liverpool took place in London because of wartime circumstances. That loss was more than compensated by the pleasure of the 1961 meeting which was organized with unobtrusive efficiency. The members of the Association are grateful to Dr. Bamber, Dr. Douglas Freshwater (Local Secretary) and their Liverpool colleagues for providing a varied, instructive and entertaining programme.

The next Annual meeting of the Association will be held in Edinburgh in 1962 on a date yet to be decided.

CORRESPONDENCE.

*The Editor, 'The British Journal of Dermatology,'
85 Harley Street, London, W.1.*

SIR,—During the past few years many boys from a Borstal Institution in this area have been referred to hospital for the treatment of severely disfiguring acne. The worst forms of acne are relatively uncommon in this essentially agricultural region (Rook, 1957, *Trans. St. John's Hosp. Derm. Soc., Lond.*, **39**, 37) and the severity of the condition in these young delinquents perhaps made a greater impression than might have been the case in a clinic in an industrial city. The possibility of some association between severe acne and delinquent behaviour was tentatively discussed with medical and criminological colleagues. Dr. L. Radzinowicz, Professor of Criminology in the University of Cambridge, considered that the question was worthy of investigation and encouraged the preliminary enquiries which form the subject of this short article.

The Medical Officer to the Borstal Allocation Centre, Dr. J. Graham, in reply to a request for information, wrote "there is no doubt whatever that many of the more disfiguring dermatoses, such as acne, have a very definite bearing on a lad's behaviour." Dr. D. J. West of the Department of Criminology later drew our attention to the report of the Cambridge-Somerville Youth Study (McCord, McCord and Zola, 1959, *Origins of Crime*, New York: Columbia University Press). In this very carefully planned investigation 506 boys in and around Boston, U.S.A., considered to be maladjusted and potentially delinquent, were selected for study. Their average age was 11 when the investigation started and 28 when it was concluded. The investigation was designed primarily as a large-scale experiment in crime prevention, and whilst the main findings do not directly concern us, certain incidental observations are of great interest to the dermatologist. Of the entire group 39% committed at least one type of crime other than a traffic offence during the 17-year period of observation. All boys were medically examined on several occasions. There was no relationship between delinquency and low intelligence, poor general health or endocrine abnormalities. Of those boys who suffered from severe acne, however, 75% later developed criminal records ($P < 0.02$). Other body deformities, the nature of which is not specified, were not significantly connected with crime.

The possibility that the cosmetic disfigurement of severe acne may produce serious psychological effects by disturbing the development of normal social relations has long been accepted by dermatologists. Although some authorities are convinced also that emotional factors can aggravate and perpetuate acne, others (Baer and Witten, 1960, *Year Book of Dermatology*, Chicago: Year Book Publishers) maintain that their direct role in acne is a very minor one. The convincing findings of the Cambridge-Somerville Youth Study cannot however be lightly dismissed. Since other body deformities were not associated with delinquency, McCord and his colleagues conclude the acne was another manifestation of the same emotional stress which gave rise to criminality. Abrahamson's (1948, *J. nerv., ment. Dis.*, **107**, 11) investigation of psychosomatic disorders in criminal offenders would appear to support this opinion. He found that psychosomatic disorders although not more frequent were more severe in criminals than in control subjects of the same age from the same social environment.

It is clearly desirable that further carefully controlled studies of the relationship of acne and other cosmetic defects to delinquency should be carried out. Meanwhile general practitioners and school medical officers should be made more aware of the importance of competent and thorough treatment of all children with acne, and the dermatologist should not hesitate to seek the assistance of his psychiatric colleagues in severe and intractable cases. Dr. Graham wrote: "In my opinion many of these delinquents who are 'cured' by one period in a Borstal are greatly assisted by medical attention which aims at removing the 'pathological epaulettes' which so many of them wear."

ARTHUR ROOK.

Cambridge.

BOOK REVIEWS

HALLOPEAU'S PYODERMITE VEGETANTE AND PEMPHIGUS VEGETANS.*

HALLOPEAU, when he described pyodermite vegetante, thought he was recording a new disease, but afterwards he regarded it as a type of pemphigus vegetans. The views of later observers have not been unanimous, and Goldsmith (1941) *Brit. J. Derm.*, **53**, 299 discussed them when describing an example of his own. He concluded that it was "a very rare but recognisable clinical entity, not pyococcal in origin, and probably related closely to pemphigus vegetans." Degos in 1953 agreed that it was a clinical entity but unrelated to pemphigus vegetans and said it was a type of staphylococcal infection.

In the present monograph Zilberberg records his investigations of one patient with pyodermite vegetante, twenty-two with pemphigus vegetans, and an infant with dermatitis herpetiformis who at one period had vegetating lesions. The patient with pyodermite vegetante, who incidentally had lesions on the tongue similar to those of Hallopeau's first patient, underwent twenty-seven biopsies of spontaneous and experimental lesions. Coagulase positive staphylococci were recovered from the lesions, and they and staphylococci from other sources were inoculated into the skin of his patient and into controls. In two day old spontaneous pustules Zilberberg saw not only micro-abscesses stuffed with neutrophils and eosinophils, but also, particularly near the margins of the inflammatory reaction, between prickle cells, small clear spaces or fissures, apparently due to rupture of some of the tonofibrils. The cells were elongated or irregular with remains of filaments projecting from their walls and sometimes bridging the clefts. These clear spaces were also noted in experimental lesions on the patient and controls. The vegetating lesions in the child with the dermatitis herpetiformis showed the same type of fissuring which disappeared when the staphylococcal infection was cured. Another characteristic sign of staphylococcal infection was separation of epithelial cells from sweat gland glomeruli.

In pemphigus vulgaris the type of acantholysis is different; the filaments are almost entirely lost and the cells are distended. However, in some patients there were coexisting lesions that suggested a possible staphylococcal origin.

This book is well printed and has 159 illustrations, mainly photomicrographs. It should be consulted by those who are particularly interested in the problems of acantholysis.

G. W. B.

LIPIDOSES.†

AFTER an account of the biochemistry and metabolism of fats the author briefly discusses the estimation of plasma lipoproteins by ethanol fractionation, electrophoresis and ultracentrifugation, before giving an account of cutaneous and tendon exanthomas. Next follows a classification of the diseases to be considered in detail later on.

In the first group, hypercholesterolaemia—which may be primary and familial, or secondary to biliary cirrhosis or myxoedema—the blood cholesterol is raised, the neutral fat normal and the serum usually clear. The second group, hyperlipaemia—with increase in blood neutral fats giving the serum a milky appearance—may be

* *Piodermite Vegetante de Hallopeau e Pênfigo Vegetante*. B. ZILBERBERG (1960). São Paulo. Pp. 180. No publisher or price stated.

† *The Dyslipidoses*. R. FLEISCHMAJER (1960). Springfield, Ill.: Chas. C. Thomas. Oxford: Blackwell Scientific Publications. Pp. 509, 184 illus. Price £6 8s.

idiopathic, or secondary to diabetes, glycogen storage disease, nephrosis or pancreatitis. The author rightly mentions the difficulty in distinguishing between idiopathic hyperlipaemia with attacks of abdominal pain, and hyperlipaemia secondary to recurrent pancreatitis.

The second half of the book is devoted to a variety of disorders of the reticulo-endothelial system with two common factors—normocholesterolaemia and some degree of increase in tissue fats. Gaucher's disease, Niemann-Pick's disease, amaurotic family idiocy and gargoylism are considered as primary dyslipidoses. Dermatological interest is revived by the final group, which is included not as disorders of fat metabolism but because of intracellular deposits of fat in diseased tissue. Here we find not only chapters on xanthoma disseminatum and the Letterer-Siwe, Hand-Schüller-Christian and eosinophilic granuloma group, but others on naevoxanthoendothelioma, hyalinosi cutis et mucosae (lipoid proteinosis) and extracellular cholesterosis. Why, one wonders, has reticulohistiocytosis (lipoid dermatitis) been omitted; and why was necrobiosis lipoidica dismissed in one and a half pages while naevoxanthoendothelioma spreads over forty-two?

While no new facts emerge from this book it is a most valuable source of information on diseases, many extremely rare, related by little more than "lipo" or "xantho" in their names. The one irritating factor is the absence of the title of the chapter from each page, an omission which makes it difficult to find one's way about the book without constant reference to the index.

P. A. J. S.

BONNEVIE RESURGENT.*

BANGING the head against a brick wall is the common lot of dermatologists trying to find out why a patient has eczema. Anything to alleviate headache from this cause is welcome. Niels Hjorth of the Finsen Institute has followed the Danish tradition started by Bonnevie of multiple patch tests for every case of eczema. Some twenty-four routine tests are further supplemented when necessary by tests with substances suspected from the history to be the cause of the eczema. Most of the routine tests are done with substances used as local applications. In the Finsen Institute balsam of Peru is one of the two therapeutic agents most often causing positive patch tests. This somewhat surprising finding led to Hjorth's thesis for a doctorate of medicine and this remarkable book consisting of some two hundred pages on balsam of Peru, to which in two and a half years two hundred and thirty patients gave positive tests. In only forty-eight of these was the balsam of Peru thought to be the cause of the current eczema.

Hjorth has collected with terrier like pertinacity information on the physical and chemical properties and the breakdown of balsam of Peru (which comes from El Salvador). He has ferreted out (to continue the zoological figure) many of the substances in the balsam, investigated to which of these his patients were sensitive and rummaged about for cross sensitivities. The most important allergens were found in the resinous portion of the balsam. Sensitivity or cross sensitivity was found to a host of substances, including, of course, perfumes, vanilla, orange peel, cinnamon and wood tars among others.

This is the book of an enthusiast, and none the worse for that. The facts are fascinating, the pertinacity splendid and the exposition clear. It would be a dull or self-satisfied soul who could learn nothing from it.

D. I. W.

* *Eczematous Allergy to Balsams*. N. HJORTH (1961) Copenhagen: Munksgaard. Pp. 216. Price dKr. 50. Also published as Supplement 46 to *Acta derm.-venereol.*, Stockholm.

CURRENT LITERATURE.

DISSEMINATED LUPUS ERYTHEMATOSUS OF THE ALIMENTARY TRACT. J. BRUCE and W. SIRCUS. (1959) *Lancet*, i, 795.

A patient suffered from numerous attacks of small bowel obstruction over a period of three years. On the two occasions she underwent laparotomy, the small gut showed intense congestion with thickening and oedema of the bowel wall. The E.S.R. was continually raised and there was leucopenia, hyperglobulinaemia and reduced serum albumin level. She became mentally abnormal and developed painful swollen joints, lymphadenopathy and enlargement of the liver. Six months before she died, L.E. cells were found for the first time, large numbers being present in the peripheral blood. At autopsy, arterial lesions were found throughout the gut. Intestinal ileus was probably due to acute inflammation of the bowel wall, and obstruction to obliteration of the lumen by massive oedema.

R. H. M.

HISTONE : AN ESSENTIAL COMPONENT FOR THE LUPUS ERYTHEMATOSUS ANTINUCLEAR REACTION. E. J. HOLBOROW and D. M. WEIR. (1959) *Lancet*, i, 809.

The sera of patients with systemic L.E. have previously been shown by the authors to contain a factor with affinity for somatic cell nuclei of many species. In the present work they report the failure of the factor to react with the nuclear material of mature guinea-pig spermatozoa, although the precursor germ-cell nuclei take up the factor strongly. The reaction was demonstrated in fresh frozen sections of guinea-pig testis and epididymis by a fluorescent antiglobulin serum.

It is known that at the end of the maturation process in spermatogenesis nucleohistone is converted to a protamine-like substance. The present work suggests that histone is an essential component for the antinuclear reaction.

R. H. M.

POSTPARTUM PANCREATITIS WITH URTICARIA. R. A. MAIN and J. R. S. PATERSON. (1959) *Lancet*, i, 813.

Pancreatitis occurring after childbirth is a well recognized syndrome. The patient described here suffered from acute pancreatitis and urticaria six weeks after delivery. Both conditions subsided after ten days.

R. H. M.

THE ACTION SPECTRUM FOR SKIN LESIONS IN PORPHYRIA CUTANEA TARDA. I. A. MAGNUS, A. D. PORTER and C. RIMINGTON. (1959) *Lancet*, i, 912.

This patient with porphyria cutanea tarda showed abnormal reactions in the skin to light of wavebands which corresponded well to the absorption spectrum of porphyrins. Abnormal cutaneous reactions—e.g., swelling, ecchymoses, and even blistering, sometimes leading later to pigmentation, telangiectasia, and atrophy—were produced at 400 m μ with a monochromator. This point is at the region of maximal absorption, the Soret band of most porphyrins. Erythema was observed also as a result of exposures to wavebands in the visible spectrum from 410 to 600 m μ ; these responses may correspond to the lesser peaks of absorption shown by porphyrins when viewed in the visible spectrum. On the other hand, the skin reactions of the patient to ultra-violet light in the normal sunburn region (around 300 m μ) were normal. Abnormal responses to light occurred as readily in skin normally clothed as in that habitually exposed. The evidence strongly suggests that in this patient photosensitivity is initiated by porphyrins in the skin. (Authors' summary.)

R. H. M.

DISSEMINATED MALIGNANT MELANOMA TREATED WITH MANNOMUSTINE. (1959) *Lancet* i, 968.

A patient dying of disseminated melanoma was treated with a massive dose of Degranol (mannomustine hydrochloride B.C.M.) followed by reinfusion of the patient's own stored marrow. Regression of skin nodules was evident within a few days but the patient died shortly afterwards of haemorrhage into a necrotic metastasis in the cerebellum. At autopsy the liver metastases showed extensive necrosis as did those which had clinically regressed in the skin and breasts. The bone marrow showed foci of actively regenerating cells, but it was impossible to decide whether these were due to recovery from the effects of the cytotoxic agent, or repopulation by the injected marrow cells.

R. H. M.

THE COURSE OF SARCOIDOSIS AND ITS MODIFICATION BY TREATMENT. D. GERAINTJAMES and A. D. THOMSON. (1959) *Lancet*, i, 1057.

The authors followed up 200 patients with sarcoidosis; some were treated with anti-tuberculous drugs, some with systemic corticosteroids, and others were untreated. Untreated sarcoidosis either showed a high incidence of spontaneous remission or persisted unchanged. Most patients with hilar-gland enlargement and about half showing pulmonary mottling eventually cleared without treatment. Bone cysts remained unchanged in treated and untreated patients. Steroid therapy modified histological changes of sarcoid so that they became more like those occurring in a non-specific inflammatory reaction. Kveim tests were not influenced by antituberculous drugs but were sometimes depressed by steroids. No significant improvement could be attributed to antituberculous therapy. The indications for steroid therapy were principally in subacute (or transient) sarcoidosis to prevent progression to a stage of chronic irreversible fibrosis, and in the chronic disease for symptomatic relief.

R. H. M.

GRENZ RAY THERAPY. J. J. JAMBOR and J. T. VALENCIA. (1959) *Dermatologia, Mexico*, 3, 326: 4, 20.

The authors treated 210 patients with encouraging results in 92% of them. The dose recommended was 300 r-500 r at fortnightly intervals. No serious sequelae were found in a follow up period of 5 years.

Malignant lesions were biopsied through the thickest part. Frozen sections were examined and the depth of the tumour was measured. The superficial dose was calculated to give a total of 3000 r to the deepest part of the tumour. There was less reaction when the total irradiation was split into daily fractions not exceeding 12 for the thickest lesion. No recurrences have been seen.

G. W. B.

GRANULOMA ANNULARE AND MIESCHER'S GRANULOMA DISCIFORMIS ET PROGRESSIVA.J. H. FRENKEN. (1959) *Dermatologia, Mexico*, 3, 301.

A diabetic man aged 66 had symmetrical lesions on the backs of his hands, wrists and on the knees, and a lesion on the lower aspect of the left forearm. The symmetrical lesion appeared clinically to be granuloma annulare and that on the forearm resembled necrobiosis lipoidica. Sections were taken from the forearm, knees and hand. In all 3 sections the histological appearance was that of granuloma annulare. After biopsy the lesion on the hand cleared.

A woman aged 54 had a dermatosis that had generalized in eruptive phases over 4 years, sparing only the feet, palms and head. The lesions were papular, either discrete or aggregated into round oval or polycyclic patches. The histology of biopsies taken from two areas suggested Miescher's granuloma. Later biopsies taken from other areas resembled granuloma annulare and the later biopsied lesions disappeared. Frenken thinks that granuloma annulare and Miescher's granuloma are different stages of the same entity.

G. W. B.

CONGENITAL AND FAMILIAL ERYTHROKERATODERMA. A. SAUL. (1960) *Dermatologia, Mexico*, 4, 40.

Saul describes the lesions of this condition in two sisters.

G. W. B.

MULTIPLE OSTEOMATOSIS, FIBROMAS, LIPOMAS AND FIBROSARCOMAS OF THE SKIN AND MESENTERY, EPIDERMOID INCLUSION CYSTS OF THE SKIN, LEIOMYOMAS AND MULTIPLE INTESTINAL POLYPOSIS. A HERITABLE DISORDER OF CONNECTIVE TISSUE. R. J. GORLIN and A. P. CHAUDHRY. (1960) *New Engl. J. Med.*, 263, 1151.

Three families with multiple osteomas, fibromas and epidermoid cysts of the skin, and intestinal polyposis: the condition appeared to be hereditary.

A. D. P.

ALOPECIA FROM TRIMETHADIONE. J. HOLOWACH and H. V. SANDEN. (1960) *New Engl. J. Med.*, 263, 1187.

Trimethadione given to two patients with epilepsy produced reversible alopecia.

A. D. P.

DEMONSTRATION OF L. E. CELLS AT LOCAL INFLAMMATORY SITES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS. P. E. PERILLIE, C. CALABRESI and S. C. FINCH. *New Engl. J. Med.* (1960) 263, 1052.

A method of searching for L. E. cells by applying a series of coverslips to abraded skin is described. It is claimed that results show the method to be simple and as sensitive as others now in use. A. D. P.

NEURODERMATITIS ENDING IN LEUKAEMIA. P. POPCHRISTOV and G. TCHECHMEDJIEV. (1960) *Ann. Derm. Syph., Paris*, 87, 514.

The authors watched a patient for sixteen years with diffuse neurodermatitis proved clinically and histologically. He then developed a "leukemoid" reaction and later chronic lymphatic leukaemia which they believe started in the skin and was related to the chronic skin condition. F. F. H.

THE SAPROPHYTIC LIFE OF DERMATOPHYTES. R. VANBREUSEGHEM. (1960) *Ann. Derm. Syph., Paris*, 87, 481.

In 1952 the author suggested that dermatophytes might have a saprophytic existence. Since then five species, *K. ajelloi*, *M. gypseum*, "*Microsporum rouge*", *T. mentagrophytes* and *T. terrestre* have been isolated from soil. However, the majority of pathogenic dermatophytes have not been found in soil though this may be due to some defect in detecting them and does not exclude their ultimate discovery. F. F. H.

PURPURIC, PIGMENTED PAPULAR AND RETICULAR DERMATITIS SLOWLY BECOMING WIDESPREAD AND GENERALIZED. P. LE COULANT, L. TEXIER and J. MALEVILLE. (1960) *Ann. Derm. Syph., Paris*, 87, 493.

The report concerns two patients, a man and a woman, one of whom was reviewed seventeen years after his first visit to the clinic. Both presented reticular and papular purpuric and pigmented lesions most marked on the extensor surfaces almost resembling crocodile skin. The condition most closely resembled Schamberg's disease and belongs to the rather vague group of purpuric "*capillarites*". F. F. H.

DIHYDROXYACETONE (DHA) : A KERATIN COLOURING AGENT. S. BLAU, N. B. KANOF and L. SIMONSON. (1960) *Arch. Derm., Chicago*, 82, 501.

DIHYDROXYACETONE : A SUNTAN SIMULATING AGENT. H. I. MAIBACH and A. M. KLIGMAN. (1960) *Arch. Derm., Chicago*, 82, 505.

These two articles show similar results after local application of 4 or 5% solution in water or spirit and water of dihydroxyacetone, a triose sugar. After daily application for several days the skin becomes "tanned" and this can be maintained by occasional application of the solution. The colour change is due to a chemical reaction with the keratin in the skin and is independent of the action of light; it lasts until the affected layer is removed, naturally or otherwise. Unwanted reactions have not been seen. It is a useful concealing agent in vitiligo or other conditions with depigmentation. J. K.

NECROBIOSIS LIPOIDICA GRANULOMATOSIS ; NECROBIOSIS LIPOIDICA DIABETICORUM IN THE NON-DIABETIC. T. G. ROLLINS and R. K. WINKELMANN. (1960) *Arch. Derm., Chicago*, 82, 537.

The authors have studied 89 patients with necrobiosis lipoidica diabeticorum, 60 were diabetics and 29 non-diabetics. The clinical appearances were identical in the two groups but the proportion of females to males was higher in the non-diabetic than in the diabetic group and the mean age at onset was greater. The histopathology in the non-diabetic form differed from that given in the literature for the diabetic form. It is an epithelioid granulomatous reaction, at times suggesting sarcoidosis, and is similar to or identical with Miescher's granulomatosis disciformis chronica et progressiva. All the patients with the non-diabetic form had normal sugar concentrations in blood and urine and none subsequently developed diabetes. J. K.

EVALUATION OF SODIUM CHLORIDE OINTMENTS IN THE TREATMENT OF ICHTHYOSIS VULGARIS. E. EPSTEIN. (1960) *Arch. Derm., Chicago*, 82, 998.

Saline baths and application of ointment containing sodium chloride have been advocated for the treatment of ichthyosis vulgaris, but no controlled study has so far been made. In the present trial four patients with ichthyosis vulgaris were treated with sodium chloride ointment on one half of the body, and the ointment base alone on the other half. Both applications were beneficial but the addition of sodium chloride did not increase the improvement noted. J. K.

OCCUPATIONAL DISEASES OF THE NAILS. C. J. WHITE and T. LAIPPLY. (1960) *Berufsdermatosen*, 8, 125.

In a general discussion of nail diseases special consideration is given to 86 cases of proved occupational origin of the abnormality of the nails. The causes may be chemical and on rarer occasions physical agents. In damage due to x-rays longitudinal striation and atrophy and telangiectasia in the surrounding skin are found. Chemical damage occurs in tar worker, those handling solvents, bakers, preparers of salads and barmen. Leukonychia in butchers using nitrite has been described. W. G. T.

OCCUPATIONAL PORPHYRIA CUTANEA TARDA. H. IPPEN. (1960) *Berufsdermatosen*, 8, 135.

A patient with porphyria cutanea tarda previously reported was heavily exposed to lead. As there were no clinical manifestations of lead poisoning the term chronic subclinical lead intoxication was chosen. A number of causes are responsible for porphyria cutanea tarda and lead plays an important part because of its interference with porphyrin metabolism. A number of undoubted cases of bronze diabetes due to lead have been described. Professional drivers represent the largest group in an analysis of a series of cases of cutaneous porphyria. Their exposure to lead cannot be doubted. Cases of cutaneous porphyria without marked skin changes are not rare and sometimes only minor pigmentation, periorbital hypertrichosis, post-bullous milia and above all an easily damaged skin are found. In addition to lead, alcohol and light are also precipitating factors and in an individual case it must be decided which factor is mainly responsible. W. G. T.

SUBCLINICAL LEAD-INTOXICATION. H. IPPEN. (1960) *Berufsdermatosen*, 8, 139.

Prolonged exposure to lead after being unrecognized for years can lead to the damage of certain organs, particularly the liver. The further course of this subclinical lead poisoning can lead to cirrhosis which may find cutaneous expression as porphyria tarda. The skin manifestation is therefore an indirect rather than direct result of lead intoxication but the connection has to be recognized, for medico-legal purposes. W. G. T.

PORPHYRIA CUTANEA TARDA IS NOT OCCUPATIONAL. E. W. BAADER. (1960) *Berufsdermatosen*, 8, 132.

Ippen's theory that cutaneous porphyria is a manifestation of lead intoxication cannot be accepted. He makes the mistake of considering exposure to lead as meaning obligatory subclinical plumbism. No reference has ever been made to involvement of the skin in clinical cases of lead poisoning. W. G. T.

THE OCCUPATIONAL ORIGIN OF MOLLUSCUM PSEUDOCARCINOMATOSUM. (KERATO-ACANTHOMA). W. BRAUN and M. ENAYAT. (1960) *Berufsdermatosen*, 8, 61.

After a very full review of the literature on this tumour the authors discuss 30 cases studied by them. Of 18 males, 15 had definite contact with tar and mineral oils and were in open-air jobs. With 12 females this aetiological connection was less obvious but it is maintained that as they all came from rural areas and were doing garden and farm work they were undoubtedly exposed to sunlight. In view of the well known histological difficulties in diagnosis, their treatment consisted invariably of excision followed by radiotherapy. W. G. T.

BAKER'S DERMATITIS. J. A. v. PREYSS. (1960) *Berufsdermatosen*, 8, 68.

Occupational dermatitis in bakers is usually caused by flour improvers, mainly persulphate. Since legislation in 1956 no new cases of persulfate allergy were found in the Münster clinic. W. G. T.

THE TREATMENT OF OCCUPATIONAL ALLERGIC DISEASES WITH BISMUTH. A. GROS-DANOV. (1960) *Berufsdermatosen*, 8, 72.

The treatment of occupational asthma and dermatitis by means of twice weekly injections of bismuth over a period of 6-7 weeks is advocated: 50% of cases clear up, 35% improve and only 15% show no change. The course may have to be repeated after an interval of a month. Skin tests become negative after treatment in a percentage of cases and diminish in intensity in the remainder. In a large proportion of cases it is unnecessary to advise change of employment.

W. G. T.

PEMPHIGUS ACUTUS FEBRILIS GRAVIS IN INSURANCE MEDICINE WITH SPECIAL REFERENCE TO BUTCHER'S PEMPHIGUS. M. TAUGNER. (1960) *Berufsdermatosen*, 8, 187.

A butcher who had been suffering from a chronic lymphatic leukaemia with skin and mucosal lesions suffered a road accident and developed an acute infectious bullous dermatitis of which he died after 16 days. It was considered that the previous skin manifestations were due to leukaemia and an analysis of 12 cases showed that chronic leukaemia is known to produce these signs though it is often stated that they occur only in the acute disease. Examination of 37 cases of pemphigus gravis in the literature does not appear to support the suggestion that it is an occupational disease as only two of them occurred in butchers. Of 18 cases in which the occupation is stated 12 developed pemphigus acutus as the result of an accident at work and this is a fact to be remembered in future medico-legal reports.

W. G. T.

OCCUPATIONAL TRICHOPHYTON RUBRUM INFECTION. V. A. BALABANOFF. (1960) *Berufsdermatosen*, 8, 201.

In 38 cases of a total of 159 trichophyton infections seen in the University skin clinic at Sofia, hands and nails were affected, and in these cases an occupational origin was assumed. The infection was usually an ascending one from the toes with or without involvement of the groin and the palms of the hands were considered to be a site of lowered resistance in such occupations as gardeners, porters, charwomen, carpenters, locksmiths and other manual workers. The connection must be more than a coincidence. The more traumatized hand was involved more frequently. Where hands were used equally both were affected.

W. G. T.

PEMPHIGUS FOLEACEUS RESEMBLING "FOGO SALVAGEM". J. GÓMEZ ORBANEJA and A. GARCÍA PÉREZ. (1960) *Actas dermo-sifilogr.*, Madrid, 51, 4.

A man began his pemphigus foliaceus at the age of 19. The disease waxed and waned for 18 years until remission was obtained by steroids, the remission continuing for several months after steroids were withdrawn. Although the patient had always lived in Madrid, certain features resembled the Brazilian pemphigus known as "fogo salvagem". The points of similarity were the early age of onset and prolonged course, opaque corneal lesions (following blistering of the left cornea), generalized severe osteoporosis especially peripherally, presence at times of warty skin lesions and endocrine changes with gynecomastia. Although all these findings have been described in pemphigus foliaceus they are rare, being much more common in fogo salvagem.

P. I.

OCCUPATIONAL PALADON DERMATITIS IN DENTAL TECHNICIANS. H.-E. KLEINE-NATROP. (1960) *Berufsdermatosen*, 8, 301.

Dermatitis due to the basic materials of paladon (polymerised methylacrylate) is generally acknowledged. Sensitivity is usually due to the liquid monomer. It is however worthwhile to establish whether sensitivity is to the whole of the liquid complex, only to the methylacrylate or only to certain additions. The more detailed analysis often meets with difficulties as the manufacturers are reluctant to disclose information about the added substances. These are accelerators, inhibitors, stabilisers, plasticizers and catalysts. Amongst these substances we find aromatic and aliphatic amines, mercaptans, hydroquinone, resorcin, phenol, pyrogallol, pyridine, benzoic acid, fatty alcohols and glycol. Many of these substances are already well known to dermatologists as sensitizers. An increase of these monomer allergies is to be expected even if dentists rarely carry out their own prosthetic work, as the substances are used for fillings and other work carried out by the dental surgeon.

The allergy will be found in other occupations and has already been reported in the manufacture of artificial nails.

W. G. T.